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Original article

Suspicion of Lyme borreliosis in patients referred to an infectious diseases clinic: what did the patients really have?

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ABSTRACT

Objective: To evaluate the conditions behind the symptoms in patients with suspected Lyme borreliosis (LB) who were referred to an infectious diseases clinic.
Methods: In this retrospective, population-based study, we collected data from the medical records of all patients referred for infectious disease consultations in 2013 due to presumed LB from a population of 1.58 million. The patients were classified according to the certainty of LB on the basis of their symptoms, signs and laboratory results. Data on the outcomes and subsequent alternative diagnoses during the 4-year follow-up period were reviewed from all of the available patient records from public, private and occupational healthcare providers.
Results: A total of 256 patients (16/100 000) were referred as a result of suspicion of LB; 30 (12%) of 256 were classified with definite, 36 (14%) with probable and 65 (25%) with possible LB. LB was unlikely in 121 (47%) patients. A novel diagnosis was discovered in the background symptoms in 73 (29%) of patients. Previously diagnosed comorbidities caused at least some of the symptoms in 48 (19%) patients. Other explanations for symptoms were found in 81 (67%) of 121 of unlikely and 22 (34%) of 65 of possible LB patients. The spectrum of conditions behind the symptoms was quite broad and most often were musculoskeletal, neurological, psychological or functional disorders.
Conclusions: LB was unlikely in half of the patients with presumed LB. In most cases the patients had other conditions that explained their symptoms. **Elisa Kortela, Clin Microbiol Infect 2021;27:1022**

Introduction

Diagnosing Lyme borreliosis (LB) can be challenging. The most typical presentation is erythema migrans, which can be confused with erysipelas, cellulitis, tick-bite hypersensitivity reaction or tinea corporis [1–3]. Early dissemination can cause nonspecific symptoms such as myalgia, arthralgia, fatigue, fever and headache, which may appear also in viral infection [4]. Neurological complaints are present in 3% to 12% of patients with LB [5]. The most common neurological manifestation in Europe is painful lymphocytic meningoradiculitis with or without cranial nerve palsy [6–8]. In late Lyme neuroborreliosis (LNB), defined as an active disease continuing for more than 6 months, patients may experience mononeuropathy, radiculopathy, encephalomyelitis or cerebral vasculitis [6,9–14].

In addition to typical but sometimes diverse symptoms, diagnosing disseminated LB relies on serologic tests and, less frequently, *Borrelia burgdorferi* nucleic acid amplification (NAT) from cerebrospinal fluid (CSF), synovial fluid or tissue samples [15]. Serologic results can be challenging to interpret as a result of slow antibody response, failure of antibodies to decrease after treatment and false-positive findings [16]. The diagnosis and treatment of LB have attracted interest among patients and the media. The reliability of recommended two-tier serology tests and physicians' ability to diagnose this disease have been questioned [17].

Many patients with medically unexplained symptoms that may indicate LB seek diagnosis and treatment. Overdiagnosis and overtreatment of LB is common, with increased patient morbidity related to unnecessary intravenous and oral antibiotics [18,19]. The

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scientific community has recently focused on the accuracy of diagnosing LB and the complexity of irrelevant LB-related antimicrobial treatments [20,21].

The purpose of this study was to evaluate conditions behind the symptoms of presumed disseminated LB among patients with a referral for infectious disease consultation at Helsinki University Hospital in 2013. The hospital district of Helsinki and Uusimaa consists of all hospitals providing specialized healthcare in southern Finland (supplementary material). All infectious diseases referrals are centralized at Helsinki University Hospital. Local guidelines instruct physicians to refer patients with suspected disseminated LB to our tertiary-care hospital. Treatment or diagnostics due to suspected late or disseminated LB are not provided elsewhere in this region. This enabled us to study suspicious disseminated LB in a population-based sample from a catchment area with 1.58 million citizens in an LB-endemic area [22–23].

Methods

We conducted a retrospective observational population-based study including all adult (≥16 years old) patients referred to Helsinki University Hospital for presumed LB between 1 January and 31 December 2013. We evaluated patients whose referral led to an appointment at the infectious diseases outpatient clinic or inpatient ward and those whose referral was returned with a written consultation and management suggestions. There were no exclusion criteria. Each patient was identified by his or her national identity code, which is unique to each resident of Finland. This code was used to identify patients from the various registries. To ensure that all patients with disseminated LB were included in this study, we also searched Helsinki University Hospital's patient database for the International Classification of Diseases, Tenth Revision (ICD-10), code A69.2 (Lyme borreliosis) to find patients treated at another clinics (e.g. rheumatology and neurology).

All of the patients' medical records were reviewed until the end of 2017 to ascertain their persistent symptoms and subsequent treatment. Medical records were reviewed from Helsinki University Hospital, public and private primary healthcare centres, the patient's occupational health service and the Finnish Student Health Service in southern Finland. The information collected included gender, age, comorbidities, history of tick bites and erythema migrans, symptoms and signs, symptom duration, laboratory and imaging results, physiological and neurophysiological examinations, number and duration of antibiotic treatments and novel diagnoses after the referral.

After evaluating all of the collected information, the patients were classified into four groups according to the certainty of LB on the basis of the criteria developed for this study (Table 1). All novel diagnoses by the treating physicians were collected from the medical records, including the novel diagnosis for symptoms of presumed LB and other symptoms separately. A previous condition or a novel diagnosis might have explained some symptoms among the patients with definite, probable or possible LB. Previous conditions were comorbidities that were diagnosed before the referral, although a patient or a treating physician might have sought an additional explanation for their symptoms. Data collection and patient classification were conducted retrospectively by one researcher (EK), a specialist in internal medicine; difficult classifications were checked by another physician.

The method for defining the patients' *B. burgdorferi*–specific antibody levels has been previously described [25]. The first-tier antibody serum tests were *Borrelia afzelii* + VlsE IgG enzyme-linked immunosorbent assay (ELISA) and *Borrelia afzelii* IgM ELISA (Sekisui Virotech, Rüsselsheim, Germany). These tests were also used for CSF antibody testing, followed by detecting intrathecal antibody production using relative antibody measurement in the serum and CSF. Second-tier serum tests were Liaison *Borrelia* IgG and Liaison *Borrelia* IgM (Liaison *Borrelia* IgG and IgM DiaSorin, Saluggia, Italy). The sum of numeric values from the two enzyme immunoassay tests for IgG (Sekisui Virotech and DiaSorin) was used for categorization (negative <25, low concentration 25–59, intermediate 60–179, high ≥180). Antibody level categorization for high concentrations required a positive immunoblot for IgG. The sum of the IgM concentration ≥25 without IgG antibodies was categorized as low total antibody concentration. Intermediate and high antibody levels were regarded as markedly positive in the patient classification according to the certainty of LB. This diagnostic algorithm and interpretation cutoffs have been analytically and clinically validated by the Helsinki University Hospital Laboratory and further verified using clinical data. The algorithm, being purely arbitrary, is based on extensive experience with these tests.

The statistical methods are provided online in the Supplementary Material.

Table 1
Classification of patients into groups according to certainty of LB

Criteria for definite LB (criteria 1, 2 or 3 fulfilled)
1. Positive *Borrelia burgdorferi* NAT from CSF, synovial fluid or skin biopsy together with symptoms suggestive of LB.[a]
2. Intrathecal production of *B. burgdorferi*–specific antibodies and CSF pleocytosis (≥5 leukocytes/μL) together with suggestive symptoms of LNB[a] without other obvious reasons.
3. Seroconversion[b] of *B. burgdorferi* and suggestive symptoms of LB[a] without other obvious reasons.

Criteria for probable LB (criteria 1 or 2 and 3 + 4 fulfilled)
1. Markedly positive[c] *B. burgdorferi* antibody levels in serum.
2. Typical EM during previous 3 months.
3. Symptoms suggestive of LB[a] without other obvious reasons.
4. Improvement after antimicrobial treatment.[d]

Criteria for possible LB (criteria 1 or 2 fulfilled)
1. Symptoms suggestive of LB[a] without other obvious reasons and *B. burgdorferi*–specific IgG antibodies in serum.[e]
2. In absence of *B. burgdorferi*–specific antibodies, duration of symptoms <2 months, specificity of symptoms of LB and response to antimicrobial treatment.[d]

Criteria for unlikely LB (criteria 1, 2 or 3 fulfilled)
1. Absence of *B. burgdorferi* IgG antibodies in serum or CSF with symptom duration for >2 months.
2. Atypical symptoms and failure to respond to antimicrobial treatment.[d]
3. Other obvious reasons for symptoms.

CSF, cerebrospinal fluid; EM, erythema migrans; LB, Lyme borreliosis; LNB, Lyme neuroborreliosis; NAT, nucleic acid amplification.
[a] Symptoms suggestive of LNB or LB are listed in Supplementary Table S1.
[b] Increase in IgG antibodies between concurrently analysed paired serum samples: S-VlsEAbG ≥30 units and S-VlsEAbG ≥50% units (DiaSorin) together with an increase in S-BorrAbG (Sekisui Virotech).
[c] Presented in Methods. Intermediate and high antibody levels were regarded as markedly positive.
[d] Reported by patient.
[e] Sum of numeric values from two enzyme immunoassay tests (Sekisui Virotech and DiaSorin) was ≥25.

This study was approved by the research board of the inflammation centre at the Helsinki University Hospital. The use of patient records of the municipal health centres, occupational healthcare centres, the Finnish Student Health Service and private healthcare clinics was approved by the Finnish Institute for Health and Welfare. The Social Insurance Institution provided information on all antimicrobial purchases from pharmacies of all of the patients included in this study. Because of the retrospective nature of this study, no ethical approval was necessary.

Results

The total number of patients with a referral due to LB suspicion to Helsinki University Hospital's Infectious Diseases Clinic in 2013 was 256 (16/100 000 population). The search of Helsinki University Hospital's database for ICD-10 code A69.2 did not reveal any LB patients who did not consult an infectious diseases specialist. Among all of the patients with a referral, 167 (65%) were called for a visit at the infectious diseases clinic, and 89 (35%) referrals were returned with a written consultation reply by an infectious disease specialist to the remitting physician mostly in general practise but also in neurology or rheumatology (Supplementary Table S2). Most (59%) of the referrals were sent between July and November (Supplementary Fig. S1).

According to the referral and review of the patients charts until the end of 2017, 30 (11.7%) and 36 (14.1%) were categorized as having definite and probable LB respectively (Fig. 1). The numbers of patients with possible or unlikely LB were 65 (25.4%) and 121 (47.3%) respectively. In four patients (1.6%), the certainty of LB could not be determined as a result of a lack of sufficient information on the clinical picture and serologic tests. Data of these four patients were excluded from the between-group comparisons.

The patients' mean age was 53.2 years (standard deviation 15.0 years, range 16–85 years), and 164 (64%) were female (Table 2). There were more female subjects in the group with unlikely LB than in the group with definite LB (p 0.009). The median duration of symptoms before referral was 3 months (range, 0–520 months). The duration of symptoms was longer in the group with unlikely LB than in the group with definite or probable LB ($p < 0.001$ and 0.012 respectively). In addition, patients with definite LB had a statistically significantly shorter duration of symptoms than did the possible LB (p 0.002) and probable LB (p 0.006) groups. Comparisons between the groups' baseline characteristics are shown in Supplementary Table S3.

Among the 30 patients with definite LB, 93% had symptoms that could be classified as suggestive of LB based on the literature, whereas the proportion of such symptoms were found in 50% to 52% of the patients in the other groups (Supplementary Tables S1 and S4). The most typical signs and symptoms among the patients with definite LB included facial palsy, radiculitis and paraesthesia (Table 3). Arthralgia was reported by approximately half of the patients in the other LB certainty groups and was more common than in definite LB. Otherwise, the symptoms varied, with no common element (Table 3).

A CSF specimen was taken from 115 patients (45%), with normal findings in 77 (67%) (Table 4). In the group with unlikely LB, 76% of the patients had negative or low antibodies, and only 13% of the patients had intermediate or high serum *B. burgdorferi* antibody levels. However, low antibody levels were also common in the other groups. The second-tier test was conducted in 188 patients. *B. burgdorferi* NAT was positive in 1 of 77, 0 of 3 and 2 of 4 of the analysed CSF, synovial fluid and skin lesion specimens respectively.

The presumed LB symptoms caused at least one follow-up contact with the healthcare system after the consultation reply or the initial visit at the infectious diseases clinic in 108 patients (89%) with unlikely LB, 57 (88%) with possible LB, 35 (97%) with probable LB, 27 (90%) with definite LB and 2 (50%) with unknown certainty of LB. Diagnostic conclusions based on the follow-up of 256 patients are presented in Fig. 1. Alternative novel conditions or diagnoses that partially explained some or most of the symptoms mentioned in the referral were found in 73 patients (29%). In 107 patients (42%), symptoms were at least partly explained by previous or novel diagnoses; only 31 patients (12%) did not have an obvious reason that could explain their symptoms. Among the patients with unlikely LB, 67% had either a previous condition or a novel diagnosis explaining their symptoms. Previous and novel diagnoses behind the symptoms are presented in Table 5 and Supplementary Tables S7 and S8.

Discussion

We evaluated the probability of LB along with other reasons during a 4-year follow-up for the symptoms in 256 patients who were referred to infectious disease specialist consultations due to

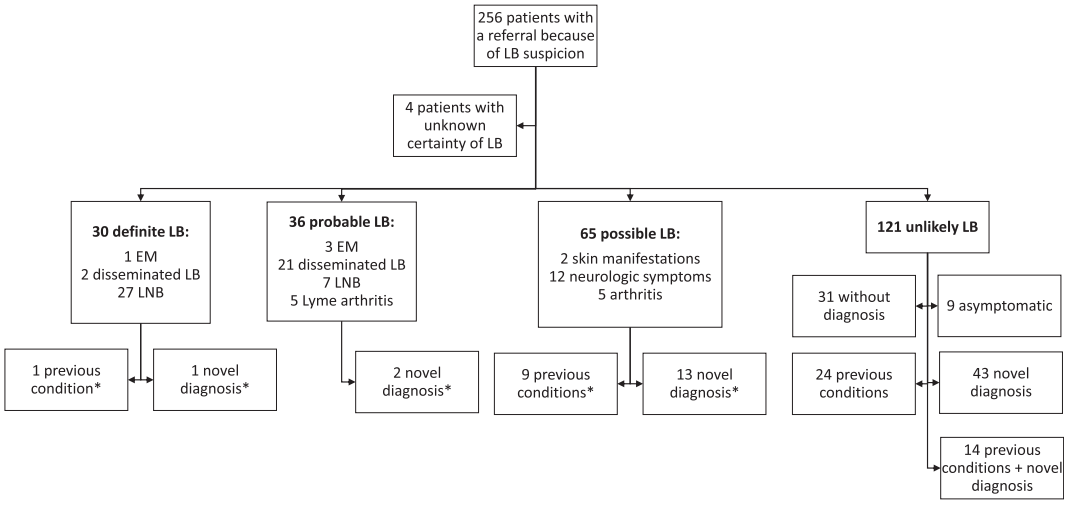

Fig. 1. Classification of patients referred for suspicion of Lyme borreliosis (LB) according to certainty of LB and number of patients with previous and novel diagnoses or conditions revealed in follow-up from patient records that could explain symptoms behind referral. *Explains part of the symptoms. EM, erythema migrans; LB, Lyme borreliosis; LNB, Lyme neuroborreliosis.

Table 2
Baseline characteristics of patients referred for consultation due to suspicion of LB categorized according to probability of LB in final analysis after 4-year follow-up of patient records ($n = 256$)

Characteristic	Definite LB ($n = 30$)	Probable LB ($n = 36$)	Possible LB ($n = 65$)	Unlikely LB ($n = 121$)	Certainty cannot be determined ($n = 4$)
Female gender	13 (43.3)	21 (58.3)	39 (60.0)	89 (73.6)	2 (50)
Age (years), mean (SD)	51.8 (16.4)	56.7 (14.2)	55.6 (14.7)	51.1 (15.0)	53.8 (15.2)
No. of coexisting diseases, median (IQR)	1 (0.75–3)	1 (0–3)	1 (1–2.5)	2 (1–3)	1.5 (0.3–2.8)
Tick bite during past year	9 (30)	15 (41.7)	29 (44.6)	35 (28.9)	2 (50)
EM during past year					
Singular	6 (20)	18 (50.0)	13 (20.0)	15 (12.4)	1 (25.0)
Multiple	0	3 (8.3)	3 (4.6)	1 (0.8)	0
Rash atypical for EM	2 (6.7)	0	7 (10.8)	15 (12.4)	1 (25.0)
Duration of symptoms (months), median (IQR)	1 (0.5–2.1)	3 (1–4.8)	3 (1–10)	6 (2–24)	0 (0–7.5)
No. of symptoms, median (IQR)	3 (2–6)	3 (2–4)	3 (2–4)	3 (2–5)	0 (0)
Principal manifestations according to referral					
No information	0	0	0	1 (0.8)	1 (25.0)
Cutaneous	1 (3.3)	3 (8.3)	2 (3.1)	6 (5.0)	2 (50.0)
Joint symptoms	0	6 (16.7)	16 (24.6)	22 (18.2)	0
Acute dissemination	3 (10.0)	15 (41.7)	22 (33.8)	25 (20.7)	0
Neurological symptoms	26 (86.7)	10 (27.8)	22 (33.8)	36 (29.8)	0
Nonspecific symptoms	0	2 (5.6)	2 (3.1)	23 (19.0)	1 (25.0)
Asymptomatic seropositive	0	0	0	8 (6.6)	0
Reason for referral was something else	0	0	1 (1.5)	0	0
Antimicrobial treatment effective for LB before referral[a]	3 (10.0)	6 (16.7)	10 (15.4)	31 (25.6)	2 (50.0)
Patient was evaluated at infectious diseases clinic	24 (80.0)	30 (83.3)	51 (78.5)	62 (51.2)	0

Data are presented as n (%) unless otherwise indicated.
EM, erythema migrans; LB, Lyme borreliosis.
[a] Described in Supplementary Materials.

Table 3
Symptoms of patients referred for consultation because of suspicion of LB ($n = 252$).

Symptom	Definite LB ($n = 30$)	Probable LB ($n = 36$)	Possible LB ($n = 65$)	Unlikely LB ($n = 121$)	p
Facial nerve palsy	18 (60)	1 (2.8)	3 (4.6)	3 (2.5)	<0.001[a]
Diplopia	6 (20)	0	0	4 (3.3)	<0.001[a]
Other peripheral nerve palsy	2 (6.7)	1 (2.8)	2 (3.1)	5 (4.1)	0.862
Radiculitis	11 (36.7)	2 (5.6)	5 (7.7)	1 (0.8)	<0.001[a]
Peripheral neuropathy	2 (6.7)	0	1 (1.5)	1 (0.8)	0.145
Paraesthesia	10 (33.3)	5 (13.9)	20 (30.8)	38 (31.4)	0.174
Monoarthritis	0	3 (8.3)	4 (6.2)	6 (5.0)	0.487
Oligoarthritis	0	1 (2.8)	1 (1.5)	4 (3.3)	0.875
Headache	9 (30.0)	10 (27.8)	17 (26.2)	43 (35.5)	0.575
Neck and shoulder pain	5 (16.7)	5 (13.9)	5 (7.7)	11 (9.1)	0.441
Myalgia	7 (23.3)	17 (47.2)	23 (35.4)	48 (39.7)	0.2277
Arthralgia	3 (10.0)	20 (55.6)	36 (55.4)	52 (43.0)	<0.001[a]
Fatigue	9 (30.0)	18 (50.0)	26 (40.0)	47 (38.8)	0.427
Vertigo	6 (20.0)	4 (11.1)	12 (18.5)	24 (19.8)	0.721
Hypoacusis	1 (3.3)	1 (2.8)	0	3 (2.5)	0.483
Tinnitus	0	1 (2.8)	0	2 (1.7)	0.604
Muscle weakness	3 (10.0)	5 (13.9)	3 (4.6)	22 (18.2)	0.056
Nausea	4 (13.3)	1 (2.8)	4 (6.2)	11 (9.1)	0.400
Weight loss	2 (6.7)	0	2 (3.1)	10 (8.3)	0.202
Flulike symptoms	4 (13.3)	1 (2.8)	5 (7.7)	5 (4.2)	0.224
Fever (temperature >38°C)	6 (20.0)	6 (16.7)	4 (6.2)	10 (8.3)	0.092
Subjective memory difficulties	4 (13.3)	1 (2.8)	3 (4.6)	10 (8.3)	0.339
Objective memory difficulty	0	1 (2.8)	2 (3.1)	2 (1.7)	0.707
Confusion	1 (3.3)	0	0	1 (0.8)	0.384
Heart conduction system disturbances	0	2 (5.6)	0	0	0.034[a]
Arrhythmia	0	0	2 (3.1)	4 (3.3)	0.762
Iritis or conjunctivitis	0	2 (5.6)	4 (6.2)	2 (1.7)	0.190
Disturbances in vision	4 (13.3)	1 (2.8)	5 (7.7)	6 (5.0)	0.297
Symptoms appear as episodes	2 (6.7)	0	3 (4.6)	12 (9.9)	0.088

Data are presented as n (%). Patients with unknown certainty are not reported here because of lack of information about symptoms and small number in group.
LB, Lyme borreliosis.
[a] Further comparison between groups is presented in Supplementary Table S5.

Table 4
Diagnostic procedures of patients suspected to have LB ($n = 252$).

Characteristic	Definite LB ($n = 30$)	Probable LB ($n = 36$)	Possible LB ($n = 65$)	Unlikely LB ($n = 121$)
Borrelia burgdorferi antibody levels in serum[a]				
Not enough information	1 (3.3)	1 (2.8)	6 (9.2)	12 (9.9)
Negative	0	0	3 (4.6)	36 (29.8)
Low positive	1 (3.3)	6 (16.7)	22 (33.8)	56 (46.3)
Intermediate	19 (63.3)	14 (38.9)	26 (40.0)	12 (9.9)
High positive	5 (16.7)	15 (41.7)	8 (12.3)	4 (3.3)
Seroconversion	4 (13.3)	0	0	1 (0.8)
CSF sampling	$n = 29$ (96.7)	$n = 9$ (25.0)	$n = 33$ (50.8)	$n = 44$ (36.4)
Normal	2 (6.9)	7 (77.8)	27 (81.8)	41 (93.2)
Pleocytosis, normal AI	0	1 (11.1)	4 (12.1)	3 (6.8)
No pleocytosis, positive AI	0	1 (11.1)	2 (6.1)	0
Pleocytosis and positive AI	27 (93.1)	0	0	0
ENMG	$n = 5$ (16.7)	$n = 2$ (5.6)	$n = 8$ (12.3)	$n = 18$ (14.9)
No information				1 (5.6)
Normal	1 (20.0)	1 (50.0)	2 (25.0)	10 (55.6)
Abnormal[b]	4 (80.0)	1 (50.0)	6 (75.0)	7 (38.9)
EEG	$n = 1$ (3.3)		$n = 1$ (1.5)	$n = 5$ (4.1)
Normal	0	0	0	3 (60.0)
Abnormal[b]	1 (100)	0	1 (100)	2 (40.0)
Brain MRI	$n = 11$ (36.7)	$n = 2$ (5.6)	$n = 7$ (10.8)	$n = 22$ (18.2)
Unknown result	1 (9.1)	0	0	1 (4.5)
Normal	3 (27.3)	2 (100)	6 (85.7)	19 (86.4)
Abnormal[b]	7 (63.6)	0	1 (14.3)	2 (9.1)
Brain MRI + MRA (with normal findings)	0	0	1 (1.5)	2 (1.7)
Cervical spine MRI	$n = 1$ (3.3)			$n = 4$ (3.3)
Normal	0	0	0	0
Abnormal[b]	1 (100)	0	0	4 (100)
Lumbar spine MRI	$n = 1$ (3.3)		$n = 1$ (1.5)	$n = 3$ (2.5)
Normal	1 (100)	0	1 (100)	2 (66.7)
Abnormal[b]	0	0	0	1 (33.3)
Whole spinal column MRI	$n = 2$ (6.7)			$n = 2$ (1.7)
Normal	0	0	0	2 (100)
Abnormal[b]	2 (100)	0	0	0
Foot MRI with abnormal result	0	0	0	1 (0.8)
Neuropsychological tests	$n = 1$ (3.3)	$n = 1$ (2.8)	$n = 2$ (3.1)	$n = 11$ (9.1)
Normal	0	0	0	3 (27.3)
Slightly abnormal[b]	1 (100)	0	1 (50.0)	6 (54.5)
Abnormal[b]	0	1 (100)	1 (50.0)	2 (18.2)

Data are presented as n (%). These diagnostic procedures were performed mainly between autumn 2012 and spring 2014.
AI, (anti-*Borrelia*) antibody index; CSF, cerebrospinal fluid; EEG, electroencephalogram; ENMG, electroneuromyography; LB, Lyme borreliosis; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.
[a] Sum of numeric values from two enzyme immunoassay tests for IgG (Sekisui Virotech and DiaSorin) was used for categorization (negative < 25, low positive 25–59, intermediate 60–179, high ≥180 and additionally positive immunoblot for IgG). Sum of numeric IgM concentration ≥25 without IgG antibodies was categorized as a low total antibody concentration. Data from *Borrelia* IgG and IgM immunoblots are presented in Supplementary Table S6.
[b] Including all kinds of abnormal changes not specific to LB.

suspected LB in 2013. Definite or probable LB was diagnosed among 26% of the patients and possible LB in 25% of the patients. LB was unlikely in 47% of the patients. The symptoms varied widely, but the patients classified with unlikely LB had significantly longer symptom duration than those who were classified with definite or probable LB. In 42% of the patients, either a previous or novel condition at 4-year follow-up explained some or all of their original referral symptoms.

In 2013, laboratories in the area near Helsinki University Hospital reported 556 serologic or NAT findings of *B. burgdorferi* to the National Infectious Disease Registry (NIDR)—more than double the number of cases referred to our centre [26]. However, all of the serologic findings in the NIDR do not represent disseminated LB, and despite instructions, many specimens were obtained from patients with erythema migrans only or from patients without symptoms of LB. Some of the patients with disseminated cases may also have been treated elsewhere.

In a previous epidemiologic study in Finland, the incidence of LNB was 2.4/100 000 in 2011, and the incidence of Lyme arthritis did not exceed 1.0/100 000 in 1996–2014 [23]. We assume that most LNB cases were treated at our hospital, so this led to an LNB (definite and probable) incidence of 2.2/100 000 in 2013. The portion of LNB from laboratory-confirmed cases was 6%. LNB was seven times more frequent than Lyme arthritis in our patients even though patients treated in the rheumatology clinic were included.

The strengths of our study are its population-based approach of disseminated LB, 4-year follow-up and comprehensive access to patient records from several different caregivers. Our patient cohort differed from other recent studies concerning confirmation of LB diagnosis [18,20,27,28]. The proportion of definite, probable and possible LB patients was higher (51%) in our patient cohort than the 13% to 23% reported in those studies. Furthermore, only 20% of our patients had been prescribed previous antimicrobial treatment effective for LB before referral compared to 50% to 85% in previous studies [18,20,27,28]. This might reflect our local guidelines to refer suspected disseminated LB for an infectious disease specialist consultation.

As expected, among the patients with definite or probable LB, only four (6%) of 66 had other conditions that partly explained their symptoms. In patients with possible LB, 34% had another underlying condition causing some of their symptoms. In 67% of patients with unlikely LB, other conditions were most likely behind their symptoms. Our data support the notion that when clinical and laboratory judgement demonstrates unlikely LB, other causes of the patient's symptoms should be actively assessed.

Table 5
Reasons for symptoms (novel diagnoses and previous conditions)

Reason	Diagnosis (n = 177)
Musculoskeletal problems	60 (33.9)
Degenerative spinal disease	19
Osteoarthritis	18
Degenerative tendinopathy (e.g. rotator cuff injury)	8
Nonspecific musculoskeletal pain	8
Overuse injuries (e.g. tennis elbow)	5
Ulnar nerve compression	1
Hypermobility syndrome	1
Neurological pathologies	22 (12.4)
Tension-type headache	5
Migraine	5
Parkinson disease	2
Normal pressure hydrocephalus	2
Demyelination in central nervous system	1
Alzheimer disease	1
Morton neuroma	1
Small fibre neuropathy	1
Axial myopathy	1
Amyotrophic lateral sclerosis	1
Nonspecific cervical syringomyelia	1
Multiple sclerosis	1
Psychiatric disorders	18 (10.2)
Depression	7
Somatic symptom disorder	3
Alcohol use disorder	2
Posttraumatic stress disorder	1
Attention deficit hyperactivity disorder	1
Insomnia, nonorganic	1
Panic disorder	1
Personality disorder	1
Nonspecific dissociative disorder	1
Functional disorders	15 (8.5)
Fibromyalgia	11
Chronic fatigue syndrome	3
Hypersomnia	1
Rheumatologic diseases	14 (7.9)
Reactive arthritis	4
Rheumatoid arthritis	3
Oligoarthritis seronegative	2
Ankylosing spondylitis	1
CREST syndrome	1
Sjögren syndrome	1
Psoriatic arthritis	1
Polymyalgia rheumatica	1
Other infectious diseases	9 (5.1)
Meningoencephalitis of unknown origin	2
Tick-borne encephalitis	1
Syphilis	1
Cellulitis	1
Pneumonia	1
Sinusitis	1
Cytomegalovirus infection	1
Chronic hepatitis C virus infection	1
Dermatologic diseases	9 (5.1)
Lymphocytoma cutis	2
Psoriasis	1
Erythema annulare	1
Eczema nummular	1
Atopic dermatitis	2
Granuloma annulare	1
Capillary malformations (port wine stains)	1
Otorhinolaryngologic diseases	8 (4.5)
Benign positional vertigo	3
Bell palsy	3
Sensorineural hearing loss	1
Sialadenitis	1
Gastroenterologic diseases	5 (2.8)
Chronic *Helicobacter pylori* gastritis	2
Coeliac disease	1
Alcoholic liver cirrhosis	1
Gastroesophageal reflux disease	1
Ophthalmologic diseases	4 (2.3)
Retinal detachment	2
Dry eyes	1
Iritis	1
Cardiovascular diseases	4 (2.3)
Atrial fibrillation	2
Coronary artery disease	1
Chronic peripheral venous insufficiency	1
Cancer	3 (1.7)
Tonsillar cancer	1
Ovarian cancer and peritoneal carcinomatosis	1
Basal-cell carcinoma	1
Other	6 (3.4)
Sleep apnoea	3
Idiopathic angio-oedema	1
Hypophysitis with panhypopituitarism	1
Previous brain injury	1

Data are presented as n (%) of new diagnoses.

Causes of symptoms in the patients with unlikely LB were variable but were similar to those previously reported [18,27]. Musculoskeletal problems, neurological pathologies and psychiatric disorders were the most common reasons. In addition, three cases of malignancy were found, which was previously demonstrated to be one caveat [29]. Some of our patients needed rapid therapy for their underlying disease, which included coronary artery disease, pneumonia or cellulitis. Our results amplify the importance of appropriate differential diagnoses among these patients. Frequent and prolonged antimicrobial treatments for suspicion of LB has been associated with adverse events and might delay necessary diagnostic procedures and treatment of underlying causes [19,30,31].

Our study has some limitations. As with all retrospective studies, the information collected might be incomplete. In our study, this came into question, especially in the documentation of the patients' symptoms and signs. Some of the symptoms might have been dismissed despite thorough patient assessment and review of the patient records from all caregivers that could be contacted. It is also possible that all of the novel diagnoses were not registered in the patient records or were not assessed using the proper criteria. In addition, our population-based setup is based on the assumption that all disseminated forms of LB were treated in our hospital. We did not search data from the entire population, leading to the possibility that we missed some cases. Also, we did not have the opportunity to follow patients who moved to another region during the follow-up period. The exact number of patients lost to follow-up is unknown, but 89% of the patients had at least one follow-up healthcare contact.

In conclusion, only half of the patients with a referral due to suspicion of LB had definite, probable or possible LB. The patients with unlikely LB had other conditions in 67% of cases that explained their symptoms, but at 4-year follow-up, 12% of all referred patients with a suspicion of LB had not received an explanation for their symptoms.

Transparency declaration

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and CSL Behring outside the submitted work. JO reports no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.09.022.

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